ASCEPT LECTURE – CHAIR: EVAN BEGG

1.1 PLENARY SPEAKER

THE HIGHS (β_{1H}) AND LOWS (β_{1L}) OF HUMAN HEART β_1-ADRENOCEPTORS (AR). P Molenaar (1,2), P Klenowski (2), AB Semmler (2), K Chee (2), M Iconomou (2), N Tugiono (3), H Kiriazis (3), Q Xu (3), XJ Du (3), U Ravens (4), T Christ (4) & A Kaumann (5) (1) Department of Medicine, Univ of Queensland, Qld 4032, (2) Institute of Health and Biomedical Innovation, QUT, Qld 4059, (3) BakerIDI Heart and Diabetes Institute, Vic 3004, (4) Department of Pharmacology and Toxicology, Dresden Univ of Technology, Germany & (5) Department of Physiology, Development and Neuroscience, Univ of Cambridge, Cambridge, UK

The β_1AR has two binding sites which can be activated to cause cardiostimulation. The first, termed, β_{1H}AR (high affinity site β_1AR) is activated by noradrenaline and adrenaline and is blocked by relatively low concentrations of β-blockers including carvedilol. The other, termed, β_{1L}AR (low affinity site β_1AR) has lower affinity for adrenaline and noradrenaline and is activated by some β-blockers including CGP12177 and pindolol at higher concentrations than those required to block the receptor. (-)-CGP12177 is a non-conventional partial agonist that causes modest and transient increases of contractile force in human atrial trabeculae. These effects are markedly increased and maintained by inhibition of phosphodiesterase PDE3. The stimulant effects of (-)-CGP12177 at human β_1ARs were verified with recombinant receptors (Kaumann and Molenaar, 2008). However, Skeberdis et al (2008) proposed that the positive inotropic effects of CGP12177 are mediated through β_3ARs in human right atrium. This proposal was not consistent with the lack of blockade of (-)-CGP12177 inotropic effects or increases in L-type Ca^{2+} current ($I_{Ca\text{-}L}$) by the β_3AR blocker LY748,337 (1 μM, Christ et al, 2010). In contrast, (-)-CGP12177-evoked increases in inotropic effects and $I_{Ca\text{-}L}$ were blocked by (-)-bupranolol 1-10 μM (Christ et al, 2010). Chronic infusion of (-)-CGP12177 (10 mg/Kg/24 hours) for 4 weeks in a mouse model of left ventricular hypertrophy induced by aortic constriction caused increases in ventricular wall thickness, fibrosis- and inflammation-related gene expression levels. β-Blockers with cardiostimulant effects mediated through β_{1L}AR could potentially be harmful in cardiac disease.

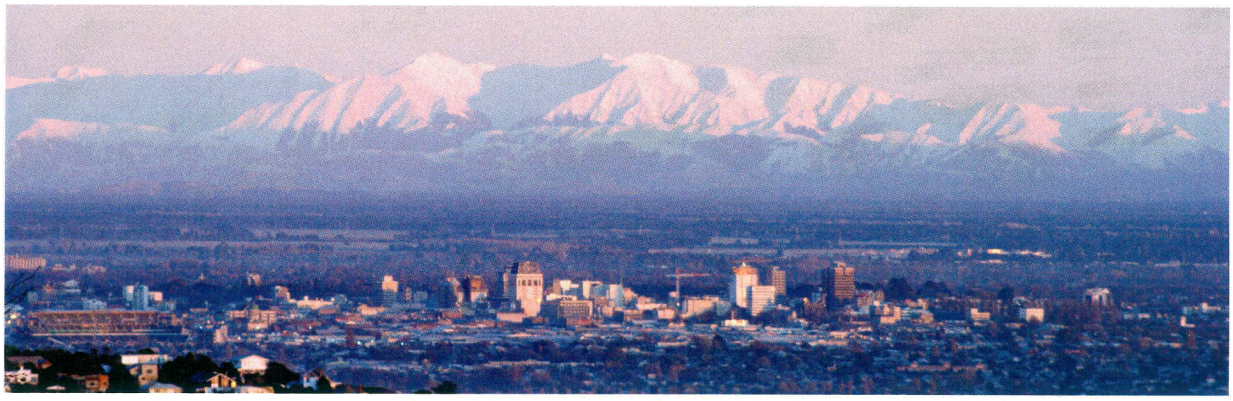
Christ T et al (2010) Br J Pharmacol, In press
Kaumann A and Molenaar P (2008) Pharmacol Ther 118, 303-336
Skeberdis VA et al (2008) J Clin Invest, 118, 3219-3227

Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists

and

Carney Symposium

New Zealand Annual Scientific Meeting



Beaven Lecture Theatre

University of Otago, Christchurch

29 – 31 August 2010

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